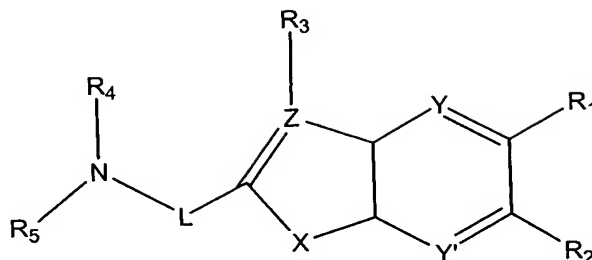


WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

5 or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof, wherein:

X is O, S, NH, or N(alkyl);

Y, and Y' are each independently selected from the group consisting of CH,

CF, and N;

10 Z is C or N, provided that when X is O or S, Z is N;

one of R₁ and R₂ is selected from the group consisting of aryl, heteroaryl, and heterocycle;

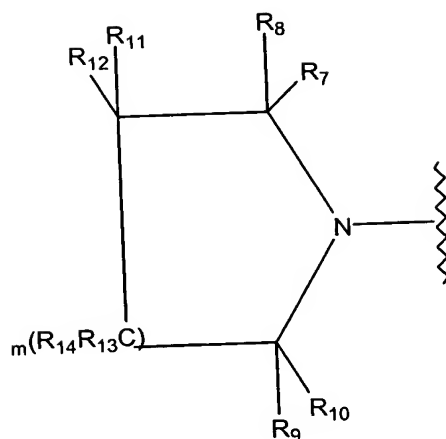
the other of R₁ and R₂ is selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, cycloalkyl, halo, cyano, and thioalkoxy;

15 R₃ is absent when Z is N and, when present, R₃ is selected from the group consisting of hydrogen, methyl, alkoxy, halo, and cyano;

R₄ and R₅ are each independently selected from the group consisting of alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, and cycloalkylalkyl, or R₄ and R₅

taken together with the nitrogen atom to which each is attached form a non-aromatic

20 ring of the structure (a):



(a) ;

R₇, R₈, R₉, and R₁₀ are each independently selected from the group consisting of hydrogen, hydroxyalkyl, fluoroalkyl, and alkyl; or one of the pair R₇ and R₈ or the pair R₉ and R₁₀ is taken together to form a C₃-C₆ ring, wherein 0, 1, or 2 heteroatoms selected from O, N, or S replace a carbon atom in the ring;

R₁₁ and R₁₂ are each independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, alkyl, and fluoro;

R₁₃ and R₁₄ at each occurrence are independently selected from the group consisting of hydrogen, alkyl, and fluoro;

L is $-[C(R_{15})(R_{16})]_n-$;

R₁₅ and R₁₆ at each occurrence are independently selected from the group consisting of hydrogen, alkyl, alkoxy, and fluoro;

m is an integer from 0-3; and

n is an integer from 2-3.

2. The compound of claim 1, wherein R₁ is aryl or heteroaryl.

3. The compound of claim 1, wherein R₁ is heteroaryl.

4. The compound of claim 1, wherein R₁ and R₂ are each independently selected from the group consisting of furyl, imidazolyl, isoxazolyl, isothiazolyl,

oxadiazolyl, oxazolyl, nicotinyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridazinonyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl, triazolyl, azepanyl, azetidiny, aziridinyl, azocanyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, pyrrolinyl, thiomorpholinyl, tetrahydrofuryl, tetrahydropyranyl, benzothienyl, isoquinolyl, indolyl, indolizin-2-yl, indazolyl, imidazo[1,2-a]pyridin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, 3-oxo-2H-pyridazin-2-yl, quinolyl, and 2-oxo-1H-pyridin-1-yl.

5. The compound of claim 1, wherein R_1 is selected from the group consisting of substituted phenyl, unsubstituted phenyl, substituted pyridine, and unsubstituted pyridine.

6. The compound of claim 1, wherein R_1 is selected from the group consisting of cyanophenyl, chlorophenyl, fluorophenyl, nicotinyl, pyridinyl, and quinolyl.

7. The compound of claim 1, wherein L is selected from the group consisting of -CH₂CH₂- or -CH₂CH₂CH₂-

8. The compound of claim 1, wherein R_3 is hydrogen or methyl.

9. The compound of claim 1, wherein R_4 and R_5 taken together with the nitrogen atom to which each is attached form a 4- to 7-membered non-aromatic ring represented by formula (a).

10. The compound of claim 1, wherein the 4- to 7-membered non-aromatic ring is selected from the group consisting of azepanyl, pyrrolidinyl, and piperidinyl.

11. The compound of claim 1, wherein at least one substituent represented by R_7 , R_8 , R_9 , and R_{10} is selected from the group consisting of alkyl, halo, fluoroalkyl, and hydroxyalkyl.

12. The compound of claim 1, wherein the 4- to 7-membered non-aromatic ring is selected from the group consisting of methylpyrrolidinyl, ethylpyrrolidinyl, dimethylaminopyrrolidinyl, isopropylpyrrolidinyl, isobutylpyrrolidinyl, hydroxymethylpyrrolidinyl, and fluoromethylpyrrolidinyl.

5

13. The compound of claim 1, wherein R_4 and R_5 are each independently selected from methyl, ethyl, and isopropyl.

14. The compound of claim 1, wherein at least one substituent represented by R_7 ,

10

R_8 , R_9 , and R_{10} is hydroxyalkyl, fluoroalkyl, or alkyl.

15. The compound of claim 1, wherein one substituent represented by R_7 , R_8 , R_9 , and R_{10} is methyl, ethyl, fluoromethyl, or hydroxymethyl.

15

16. The compound of claim 1, wherein one substituent represented by R_7 , R_8 , R_9 , and R_{10} is alkyl and the other three substituents are hydrogen.

17. The compound of claim 1, wherein R_{11} , R_{12} , R_{13} , and R_{14} are each hydrogen.

20

18. The compound of claim 1, wherein R_{13} and R_{14} at each occurrence are each independently selected from the group consisting of hydrogen and alkyl.

19. The compound of claim 1, wherein R_{15} and R_{16} are hydrogen.

25

20. The compound of claim 1, wherein m is 0, 1, or 2.

21. The compound of claim 1, wherein n is 2.

22. The compound of claim 1, wherein X is O and Z is N.

30

23. The compound of claim 1, wherein X is -NH- or -N(alkyl)- and Z is C.

24. The compound of claim 1, wherein X is -NH- or -N(alkyl)- and Z is N.

25. The compound of claim 1, wherein X is S and Z is N.

5 26. The compound of claim 1, wherein:

R₁ is heteroaryl;

R₂ and R₃ are hydrogen;

L is -CH₂CH₂-;

m is 1; and

10 R₄ and R₅ are taken together to form a pyrrolidiny ring of formula (a), wherein one of R₇, R₈, R₉, and R₁₀ is methyl and the remaining three substituents are hydrogen.

27. The compound of claim 26, wherein X is O or S and Z is N.

15

28. The compound of claim 1 selected from the group consisting of

4-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-5-yl}-benzonitrile;

3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-5-yl}-benzonitrile;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-p-tolyl-benzothiazole;

20 2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-m-tolyl-benzothiazole;

5-(4-Chloro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzothiazole;

5-(3-Chloro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzothiazole;

5-(4-Ethyl-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzothiazole;

Dimethyl-(4-{2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-5-yl}-

25 phenyl)-amine;

5-(4-Fluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzothiazole;

5-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-5-yl}-nicotinonitrile;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-6-pyridin-3-yl-benzothiazole;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-6-pyridin-4-yl-benzothiazole;

30 6-(6-Methoxy-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-

benzothiazole;

6-(3-Chloro-pyridin-4-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-
benzothiazole;

6-(2,6-Difluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-
benzothiazole;

5 2-Methyl-2'-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-[5,6"]bibenzothiazolyl;
3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-6-yl}-quinoline;
2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-6-pyrimidin-5-yl-benzothiazole;
6-(6-Fluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-

benzothiazole;

10 5-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-benzothiazol-6-yl}-nicotinonitrile;
6-(1-Methyl-1H-indol-5-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-

benzothiazole;

6-(2,6-Dimethyl-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-

benzothiazole;

15 4-{2-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
4-{2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
4-[2-(2-Pyrrolidin-1-yl-ethyl)-benzooxazol-5-yl]-benzonitrile;
4-{2-[2-(2-(S)-methyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
4-{2-[2-(3-(R)-Hydroxy-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
20 4-{2-[2-(2-(S)-Hydroxymethyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-

benzonitrile;

4-{2-[2-(2-(R),5-(R)-Dimethyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-

benzonitrile;

4-[2-(2-Piperidin-1-yl-ethyl)-benzooxazol-5-yl]-benzonitrile;

25 4-{2-[2-(2-(R)-methyl-piperidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
4-{2-[2-(2-(S)-Methoxymethyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-

benzonitrile;

4-[2-(2-Azepan-1-yl-ethyl)-benzooxazol-5-yl]-benzonitrile;

4-[2-(2-Diethylamino-ethyl)-benzooxazol-5-yl]-benzonitrile;

30 4-{2-[2-(Isopropyl-methyl-amino)-ethyl]-benzooxazol-5-yl}-benzonitrile;

4-{2-[2-(tert-Butyl-methyl-amino)-ethyl]-benzooxazol-5-yl}-benzonitrile;

4-[2-[2-(Butyl-methyl-amino)-ethyl]-benzooxazol-5-yl]-benzonitrile;

4-{2-[2-(2-Hydroxymethyl-piperidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;
4-(2-{2-[2-(2-Hydroxy-ethyl)-piperidin-1-yl]-ethyl}-benzooxazol-5-yl)-
benzonitrile;

4-{2-[2-(2-Isopropyl-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;

5 4-{2-[2-(2-(R)-Methyl-azetidin-1-yl)-ethyl]-benzooxazol-5-yl}-benzonitrile;

4-{2-[2-(2-(S)-Fluoromethyl-azetidin-1-yl)-ethyl]-benzooxazol-5-yl}-

benzonitrile;

4-{2-[2-(2-(S)-Hydroxymethyl-azetidin-1-yl)-ethyl]-benzooxazol-5-yl}-

benzonitrile;

10 4-[2-(2-Azetidin-1-yl-ethyl)-benzooxazol-5-yl]-benzonitrile;

4-(2-{2-[cis-2,6-dimethyl-piperidin-1-yl]-ethyl}-benzooxazol-5-yl)-benzonitrile;

4-(2-{2-[1,4,5,6-tetrahydropyrimidin-1-yl]-ethyl}-benzooxazol-5-yl)-benzonitrile;

4-(2-{2-[ethyl-isopropyl-amino]-ethyl}-benzooxazol-5-yl)-benzonitrile;

4-{2-[2-(2-(2-methyl-propyl)-pyrrolidin-1-yl)-ethyl]-benzooxazol-5-yl}-

15 benzonitrile;

4-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-benzonitrile;

4-{1-Methyl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-

benzonitrile;

3-{1-Methyl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-

20 benzonitrile;

3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-benzonitrile;

5-(4-Fluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5-(3,5-Difluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-(4-trifluoromethoxy-phenyl)-1H-

25 indole;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-pyridin-3-yl-1H-indole;

1-(3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-phenyl)-ethanone;

5-Furan-2-yl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5-(2,6-Difluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

30 5-(6-Methoxy-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5-(4-Methanesulfonyl-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

indole;

5-(2,6-Dimethyl-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

1-(4-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-phenyl)-ethanone;

5-(3-Fluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5 Dimethyl-(4-{2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-phenyl)-amine;

5-(4-Chloro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5-(2,4-Dimethoxy-pyrimidin-5-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

10 2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-(3-trifluoromethyl-phenyl)-1H-indole;

2-Methyl-5-{2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-benzothiazole;

8-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-quinoline;

5-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-nicotinonitrile;

15 5-(5-Methoxy-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

5-(6-Fluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indole;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-pyrimidin-5-yl-1H-indole;

1-Methyl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-5-pyridin-3-yl-1H-indole;

1-Methyl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-5-pyrimidin-5-yl-1H-indole;

20 5-{1-Methyl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-indol-5-yl}-nicotinonitrile;

4-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-benzonitrile;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-pyridin-3-yl-1H-benzoimidazole;

25 5-(4-Fluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazole;

1-(4-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-phenyl)-ethanone;

3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-benzonitrile;

30 1-(3-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-phenyl)-ethanone;

5-(3-Methoxy-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazole;

5-Furan-2-yl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazole;

5-(2,6-Difluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

5 benzoimidazole;

5-(6-Methoxy-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

5-(4-Methanesulfonyl-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

10 5-(2,4-Dimethoxy-pyrimidin-5-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

5-Benzo[1,3]dioxol-5-yl-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

5-(5-Methoxy-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

15 benzoimidazole;

5-(2,6-Dimethyl-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

4-{2-[2-(2-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-benzoic acid

methyl ester;

20 2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-(4-methylsulfanyl-phenyl)-1H-

benzoimidazole;

5-(3,5-Difluoro-phenyl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole;

2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-5-pyrimidin-5-yl-1H-benzoimidazole;

25 8-{2-[2-(2-(R)-Methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-quinoline;

Dimethyl-(4-{2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-benzoimidazol-5-yl}-

phenyl)-amine; and

5-(6-Fluoro-pyridin-3-yl)-2-[2-(2-(R)-methyl-pyrrolidin-1-yl)-ethyl]-1H-

benzoimidazole.

30

29. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

30. A method of selectively modulating the effects of histamine-3 receptors in a mammal comprising administering an effective amount of a compound of claim 1.

5 31. A method of treating a condition or disorder modulated by the histamine-3 receptors in a mammal comprising administering an effective amount of a compound of claim 1.

10 32. The method according to claim 31, wherein the condition or disorder is selected from the group consisting of acute myocardial infarction, Alzheimer's disease, asthma, attention-deficit hyperactivity disorder, bipolar disorder, cognitive enhancement, cognitive deficits in psychiatric disorders, deficits of memory, deficits of learning, dementia, cutaneous carcinoma, drug abuse, diabetes, type II diabetes, depression, epilepsy, gastrointestinal disorders, inflammation, insulin resistance, 15 syndrome, jet lag, medullary thyroid carcinoma, melanoma, Meniere's disease, metabolic syndrome, mild cognitive impairment, migraine, mood and attention alteration, motion sickness, narcolepsy, neurogenic inflammation, obesity, obsessive compulsive disorder, pain, Parkinson's disease, polycystic ovary syndrome, schizophrenia, seizures, septic shock, Syndrome X, Tourette's syndrome, vertigo, 20 and wakefulness.

33. The method according to claim 30, wherein the condition or disorder affects the memory or cognition.